FORM PTO-1390 (REV 10-94) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

13102.6USWO

U S APPLICATION NO (If known, see 37 C F R 1 5)
UNKNOWN 10/089611

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/IN00/00079	25-AUGUST-2000	1-OCTOBER-1999

TITLE OF INVENTION

AN IMPROVED PHARMACEUTICAL COMPOSITION AND A PROCESS FOR ITS PREPARATION

APPLICANT(S) FOR DO/EO/US

RAO, PAVULURI VENKATESWARA; KHADGAPATHI, PODILI

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U S.C. 371(b) and PCT Articles 22 and 39(l).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US)
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98, Form 1449, 4 references.

12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. [X] A FIRST preliminary amendment, Marked Up Version, Abstract page.
    [ ] A SECOND of SUBSEQUENT preliminary amendment.

14. [ ] A substitute specification.

15. [ ] A change of power of attorney and/or address letter.

16. [X] Other items or information: PCT/ISA/210; PCT/IB/308;PCT/IB/332; PCT/RO/101

09/089611 JC10 Rec'd PCT/PTO 29 MAR 2002

U.S. APPLICATION NO (If known, see 37 C F R 1 5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
UNKNOWN 10/089611	PCT/IN00/00079	13102.6USWO

17. [X] The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492(a) (1)-(5)):		
Search Report has been prepared by the EPO or JPO **$890.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492(a)(1)) **$710.00**		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$740.00**		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(3)) paid to USPTO **$1040.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$0**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	10 -20 =	18	X **$18.00**	**$0**	
Independent claims	3 -3 =	84	X **$80.00**	**$0**	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$260.00**	**$0**	
TOTAL OF ABOVE CALCULATIONS =				**$890.00**	
Reduction by 1/2 for filing by small entity, if applicable. Small entity status is claimed pursuant to 37 CFR 1.27				**$0**	
SUBTOTAL =				**$890.00**	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f).			+	**$0**	
TOTAL NATIONAL FEE =				**$890.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)) The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property			+	**$0**	
TOTAL FEES ENCLOSED =				**$890.00**	
				Amount to be: refunded	**$0**
				charged	**$0**

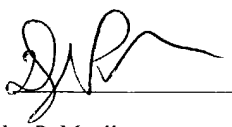
a. [X] Check(s) in the amount of $890.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-2725.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO
Douglas P. Mueller
MERCHANT & GOULD
P.O. Box 2903
Minneapolis, MN 55402-0903

SIGNATURE: 

NAME: Douglas P. Mueller

REGISTRATION NUMBER: 30,300

S/N unknown PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	RAO, et al.	Examiner:	unknown
Serial No.:	unknown	Group Art Unit:	
Filed:	March 29, 2002	Docket No.:	13102.6USW1
Title:	AN IMPROVED PHARMACEUTICAL COMPOSITION AND A PROCESS FOR ITS PREPARATION		

CERTIFICATE UNDER 37 C F R 1 10
"Express Mail" mailing label number EV077885144US
Date of Deposit March 29, 2002

I hereby certify that this paper or fee is being deposited with the U S Postal Service "Express Mail Post Office to Addressee" service under 37 C F R 1 10 on the date indicated above and is addressed to Commissioner for Patents, Washington, D C 20231

By
Name Chris Stordahl

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D. C. 20231

Dear Sir:

In connection with the above-identified application filed herewith, please enter the following preliminary amendment:

IN THE CLAIMS

Please amended the claims as follows:

3. (AMENDED) A pharmaceutical composition as claimed in claim 1 wherein the enteric polymer employed for coating the gelatin shell is selected from polymers such as hydroxypropyl methyl cellulose phthalate, alkyl methacrylate and methacrylic acid copolymers, polyvinyl acetate phthalate and the like in the form of free acid or their ammonia or alkali metal salts and the amount employed ranging from 5.0 to 40.0 percent, preferably 5.0 to 25.0 percent by weight, with reference to the dried shell.

4. (AMENDED) A pharmaceutical composition as claimed in claim 1 wherein the benzimidazole derivative in the formulation is suspended / solubilised in a hydrophobic oily substance selected from fats and oils of vegetable origin such as sesame oil, corn oil, maize oil, soybean oil, sunflower oil, arachis oil, gingly oil and the like; animal origin such as fish oil, pig oil, beef oil and the like; esters of straight chain aliphatic oils such as Sunsoft 700 P-2 (Taiho chemical company) Panasete 810 (Nippon oils and Fats); hydrogenated vegetable oils or a mixture thereof and the amount of hydrophobic oily substance used ranging from 50.0 to 80.0 percent by weight, with reference to the contents filled in capsules.

5. (AMENDED) A pharmaceutical composition as claimed in claim 1 wherein substances such ascolloidal silicon dioxide, polyvinylpyrrolidone are used as dispersing agents in an amount ranging from 0.5 to 20.0 percent preferably 1.0 to 10.0 percent by weight and materials such as glyceryl monostearate, lecithin, polyoxyethylene castor oil derivative such as Cremophor RH 40, Cremophor EL (BASF) polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulphate, docusate sodium and the like are used as surface active agent and / or a solublising agent and the amount of surface active agent and/or solublising agent ranging from 2.0 to 20.0 percent, preferably 5.0 to 15.0 percent by weight, with reference to the contents filled in capsule.

6. (AMENDED) A pharmaceutical composition as claimed in claim 1 wherein materials such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid, other suitable organic or inorganic acids; substances used in antacid preparations; meglumine; triethanolamine and the like are used as alkaline inert reacting materials and the amount ranging from 5.0 to 40.0 percent, preferably 10.0 to 25.0 percent by weight, with reference to the contents filled in capsule.

7. (AMENDED) A pharmaceutical composition as claimed in claim 1 wherein the soft gel capsules are treated with a gelatin cross linking agent such as formaldehyde, glutaraldehyde, crotonaldehyde, 1,2-phthalic acid aldehyde, 1,3-phtbalic acid aldehyde, 1,4-phthalic acid aldehyde; carboimides such as 1-ethyl-3-[2-morpholinyl-(4)-ethyl]-carboimide- metho-P-toluene-sulfonate and the like.

8. (AMENDED) A pharmaceutical composition as claimed in claim 1 wherein the soft gel capsules are treated with cold dilute solutions of acids selected from hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid, citric acid, propionic acid, benzoic acid, oxalic acid, maleic acid, fumaric acid and the like.

REMARKS

The above preliminary amendment is made to remove multiple dependencies from claims 3, 4, 5, 6, 7, and 8. Please refer to the Marked-Up claim pages 19, and 20, attached herewith.

Applicants respectfully request that the preliminary amendment described herein be entered into the record prior to calculation of the filing fee and prior to examination and consideration of the above-identified application.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' primary attorney-of record, Douglas P. Mueller (Reg. No. 30,300), at (612) 371.5237.

Respectfully submitted,

MERCHANT & GOULD P.C.
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Dated: March 29, 2002

By _____
Douglas P. Mueller
Reg. No. 30,300

DPM/rw

AN IMPROVED PHARMACEUTICAL COMPOSITION AND A PROCESS FOR ITS PREPARATION.

The present invention relates to an improved pharmaceutical composition and a process for its preparation. The present invention particularly relates to an improved pharmaceutical composition, in the form of a soft gel capsule resistant to digestive juice. The composition of the present invention is made up of gelatin and an enteric polymer in the form of free acid or its salt, containing a benzimidazole derivative used in the treatment of duodenal ulcers, solublised and/or suspended in a liquid or semisolid medium, comprising of a hydrophobic carrier, an alkaline inert reacting material and a surface active agent and/or a solublising agent. The present invention also relates to a method for preparing the above said pharmaceutical composition.

Benzimidazole derivatives such as Omeprazole, Lansoprazole Timoprazole and Pantoprazole etc., are known potent proton pump inhibitors with powerful inhibitory action against the secretion of gastric juice (Lancet, Nov. 27, 1982 pages 1223-1224). They are used in the treatment of Zollinzer – Elision syndrome and stress related esophagitis ulceration. The derivatives are well known and are described, for example in EP-A 0005129.

It has been found that these benzimidazole derivatives, and in particular omeprazole, are susceptible to degradation in acid and neutral media. It is known to protect oral dosage forms of such benzimidazole derivatives by providing an enteric coating. In this way, the active material is protected from acidic gastric juices until it reaches the desired site of release, e.g. the small intestine. Because certain enteric coatings themselves can be, or contain, acidic material, it also often is required to protect the benzimidazole derivatives from the acidity of the enteric coating. For example, it is known to formulate the benzimidazole derivatives with an alkaline material before applying the enteric coating. It is also known to provide an intermediate coating between the benzimidazole derivative and the enteric coating. Generally the intermediate coating is selected so as to be substantially water-soluble or water-dispersible.

EP-A-024 7983; US 4,786,505; US 4,853,230 and US 5,385,739 describe oral pharmaceutical preparations containing benzimidazole derivatives that are potent inhibitors of gastric acid secretion, which are composed of a core material in the form of small beads or tablets containing one of the

benzimidazole derivatives, particularly omeprazole, together with an alkaline reacting compound. The core material contains one or more inert reacting sub-coating layers thereon thereby providing a final outer enteric coating. Although the above-described compositions are reasonably stable over an extended period of storage, discoloration of the pellets and / or tablets with reduced gastric resistance and reduction of dissolution rate in alkaline buffers was observed.

Moreover the processes disclosed above are time-consuming and laborious, involving many stages in manufacturing of the composition, consequently increasing the cost of the final composition.

In a German patent DE 32 22 476 a pharmaceutical composition has been described in which a soft gelatin capsule that is resistant to digestive juice, whose wall includes a usual gelatin mass which contains polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate or a vinyl acetate / crotonic acid copolymer and/or an alkali metal salt, ammonia salt or amino salt of the same in their wall, and which released its contents readily in the intestines within the prescribed time. The capsules are further treated on the surface with an aldehyde-coating agent.

With the capsule shell composition described in DE 32 22 476 above, if used as such for manufacturing capsules containing one of the benzimidazole derivatives in a conventional manner, the free acidic groups of the polymer in the shell composition reacts with the benzimidazole derivatives and reduces the efficacy of the product during its storage / shelf life period.

The above said prior art processes also have the following drawbacks: -

Requirement of sophisticated coating equipment and large amounts of organic solvents / alkali salts are employed to dissolve the enteric polymers for coating the fine particles.

The active substance(s), benzimidazole derivatives, needs to be protected by a sub coat from the reacting acidic groups present in the enteric polymers.

The processing time and the number of steps involved are many.

The resulting product, i.e., pellets / beads / tablets, has to be dried to keep moisture content below 1.5% to ensure drug stability during processing and through its shelf storage.

The active substance(s), benzimidazole derivatives, present in the final formulation as solid dispersed in a hydrophilic solid matrix and hence requires some time to dissolve into the surrounding intestinal fluid before being absorbed.

Large quantities of polymer i.e. 15-25% w/w, based on product, need to be applied to achieve desired gastric protection.

The pH of medium used to suspend / solublise the drug needs to be adjusted to alkaline condition i.e. above pH 8.0 to prevent degradation during processing.

The micro environment surrounding the core also contains alkaline material to neutralise the acidic medium that permeates the outer enteric coating during the product transit through stomach.

In case of pellets / beads large surface area needs to be coated with protective polymer sub-coat.

Considering the importance gained for the composition containing benzimidazole derivatives, particularly for the treatment of duodenal ulcers, there is a need for the development of pharmaceutical composition containing said derivatives having stability for an extended period during which period the composition does not get discoloured and / or degraded.

The present invention is directed to the production of soft gelatin capsules in a conventional manner using gelatin mass having an enteric polymer incorporated into it and to incorporate a mixture containing benzimidazole derivative, and an alkaline reacting substance with larger quantities of hydrophobic oily substance or a mixture of such oily substances into the gelatin shell . The resulting capsules being insoluble up to a pH value of 5.5 in aqueous media, but quickly dissolving above a pH of 6.0.

The invention has been developed based on our finding as a result of sustained R & D work, that the incorporation of benzimidazole derivatives, particularly useful for the treatment of duodenal ulcers, along with an alkaline inert reacting material into a hydrophobic oily substance wherein the benzimidazole derivative is in the form of solution or dispersion, results in extended periods of stability during which period the composition does not get discolored and / or degraded.

In other words, the active ingredient in the composition is kept partially in the form of solution and partially in the form of finely divided particles suspended freely in the oily substance which makes the active ingredient readily absorbable the moment the gastric resistant but intestinal soluble gelatin composition is dissolved.

Such a composition will have an advantage over the existing form of the formulation as the available dosage forms for benzimidazole derivatives are having the total amount of active ingredient in the form of solid particles engulfed in a solid matrix of excipients preferably hydrophilic substances, further coated with protective and gastric resistant enteric polymer coatings. It may take some time to dissolve these coats before the benzimidazole derivative is dissolved into the surronding intestinal fluid and gets absorbed.

Accordingly the main objective of the present invention is to provide an improved pharmaceutical composition containing benzimidazole derivatives having enhanced stability during storage.

According to another objective of the present invention there is provided intestine dissoluble soft gel capsule composition comprising gelatin and an enteric polymer in the form of a free acid or its salt and the pharmaceutical composition comprises benzimidazole derivatives, in particular omeprazole, incorporated in an oily base which is stable during shelf storage.

Still another objective of the invention is to provide a pharmaceutical composition comprising benzimidazole derivatives, to be filled into soft gel capsules, which composition reduces degradation of the benzimidazole derivatives during storage / shelf life.

According to still another objective of the invention there is provided a process for preparation of soft gel capsules comprising benzimidazole derivatives that are resistant to the digestive / gastric juice, a gelatin mass and an enteric polymer in the form of a free acid or as its salt.

Accordingly, the present invention provides, an improved pharmaceutical composition in the form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments which comprises a gelatin shell which is resistant to gastric juice and soluble in intestine having an enteric polymer coating in the form of free acid or its salt, the capsule incorporating a composition comprising of benzimidazole derivative, a hydrophobic oily substance or a mixture of such

oily substances, an alkaline inert reacting material, a dispersing agent, a surface active agent and / or a solublising agent; the resulting capsules being insoluble in aqueous medium up to a pH of 5.5 but quickly dissolving above pH of 6.0.,

According to another feature of the present invention, there is provided a process for the preparation of a pharmaceutical composition in the form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments which comprises forming a gelatin shell which is resistant to gastric juice and soluble in intestine having an enteric polymer coating in the form of free acid or its salt, incorporating into the resultant capsule a composition comprising a benzimidazole derivative, a hydrophobic oily substance or a mixture of such oily substances, such substance(s) being insoluble in aqueous medium up to a pH of 5.5 but quickly dissolving above pH of 6.0.,an alkaline inert reacting material, a dispersing agent, a surface active agent and / or a solublising agent.

The capsules so formed are insoluble in aqueous medium up to a pH of 5.5 but quickly dissolve above pH of 6.0.

In a preferred embodiment of the invention, the enteric polymer used in the soft gel capsule composition may be selected from among the polymers but not limited to free acid forms of hydroxypropyl methyl cellulose phthalate, alkylmethacrylate and methacrylic acid ester copolymers, polyvinylacetate phthalate and the like or their ammonia or alkali metal salts. The amount of such enteric polymer employed may range from 5.0 – 40.0 percent, preferably 5.0 – 25.0 percent by weight with reference to the dried shell.

The gelatin mass into which the enteric polymer is incorporated is made up of a composition known in the art and contains gelatin, a plasticizer, preservatives, colourants, opacifiers, flavours etc., as required.

In order to carry out faster dissolution of the enteric polymer for preparing the capsule shell composition, the polymer is first dispersed in water, then an aqueous solution of ammonia or alkali metal salt is mixed while stirring. When alkali metal salt is used it may be selected from substances such as sodium hydroxide, potassium hydroxide, bicarbonate sodium, potassium bicarbonate, sodium carbonate, potassium carbonate etc. The quantity of the base materials used is such that it is sufficient to neutralise 60 to 100 percent of the free acid groups present in the selected enteric polymer.

The excess ammonia or alkali has to be removed from the capsule shell composition to avoid decomposition of the ester couplings in enteric polymers. When aqueous ammonia solution is used to prepare polymer solution, the excess ammonia has to be removed before preparing the capsule after mixing with the gelatin mass, by mixing the mass under reduced pressure in warm condition.

When alkali metal salts are used, the excess alkali is to be neutralized by treating the capsules with an acid selected from any of the following ones, hydrochloric acid, sulphric acid, nitric acid, phosphoric acid, mono carboxylic acids such as acetic acid, propionic acid, benzoic acid etc., dicarboxylic acids such as oxalic acid, maleic acid, fumaric acid etc. The acids are used in the form of cold dilute aqueous solutions in the concentration range of 3 to 30% depending on the type of acid used. The acid treatment may be carried out after manufacturing and partial drying of the capsules to avoid deformation and / or leakage of the capsule contents.

According to another feature of the invention the soft gel capsules are optionally treated with a cross-linking agent that reacts with gelatin and makes it insoluble in gastric juice. The cross-linking agent may be selected from among the aldehydes such as formaldehyde, glutaraldehyde, crotonaldehyde 1,2-phthalic acid aldehyde, 1,3-phthalic acid aldehyde, 1,4-phthalic acid aldehyde or carbodiimides like 1-ethyl-3-[2-morpholinyl-(4)-ethyl]-carbodiimide-metho-p-toluene-sulfonate. The treatment may be done by either coating 0.05 to 1.0% w/v of the substance in an alcohol containing aqueous solution on to the soft gel capsule surface or mixing these substances in the gelatin mass before capsule manufacturing.

According to another feature of the invention the pharmaceutical composition containing benzimidazole derivative, known for its potent proton pump inhibition with powerful inhibitory action against the secretion of gastric juice, is prepared by suspending and/or solubilising the benzimidazole derivative in a carrier mixture composed of a hydrophobic oily carrier material, an alkaline inert reacting material and a dispersing agent and/or a surface active agent. surface active agent. The amount of such benzimidazole derivative used is equivalent to one unit dose recommended depending on the benzimidazole derivative incorporated i.e. for omeprazole the amount incorporated into enteric soft gel capsule may range from 10.0 to 60.0mg per capsule, preferably 20.0 to 40.0 mg per capsule.

The hydrophobic oily material may be selected from among the following fats and oils: Fats and oils of vegetable origin such as sesame oil, corn, maize oil, soybean oil, sunflower oil, arachis oil, gingly oil etc.; animal oils such as fish oil, pig oil, beef oil etc.; esters of straight chained aliphatic oils contained in glycerol such as Sunsoft 700 P-2 (a monoester substance manufactured by Taiho Chemicals Company) Panasete 810 (a triester substance, manufactured by Nippon Oils and Fats); hydrogenated vegetable oils or a mixture thereof. The amount of such hydrophobic oily material may range from 50.0 to 80.0 percent by weight with reference to the contents filled in a capsule.

The alkaline buffering material present in the pharmaceutical composition may be selected from among but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminum salts of phosphoric acid, carbonic acid, citric acid, other suitable organic or inorganic acids; substances used in antacid preparations; meglumine; triethanolamine etc. The amount of such alkaline buffering material present in the composition may range from 5.0 to 40.0 percent, preferably 10.0 to 25.0 percent by weight with reference to the contents filled in capsule.

The substances that increase viscosity of the oily material either by dissolving or by forming a colloidal dispersion are used as dispersing agents. The dispersing agent is selected from among but not restricted to colloidal silicon dioxide, polyvinylpyrrolidone etc. The mount of such suspending agent present in the composition may range from 0.5 to 20.0 percent preferably 1.0 to 10.0 percent by weight with reference to the content filled in capsules.

The surface active agent used as solublising and / or dispersing agents is selected from among but is not restricted to substances such as glyceryl monostearate, polyoxyethylene castor oil derivatives such as Cremophor RH 40, Cremophor EL (Make : BASF Corporation), lecithin, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulphate, doccusate sodium etc. The amount of such surface active agent present in the composition may range from 2.0 to 20.0 percent preferably 5.0 to 15.0 percent by weight with reference to contents filled in capsule.

The seamless soft gel capsules can be manufactured on a rotary die machine filling with the liquid and / or semi solid composition containing benzimidazole derivatives.

The invention is described in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

EXAMPLE – 1

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	17.5
Water	20.0
Hydroxypropyl methyl cellulose phthalate	7.5
Ammonia solution (25%w/v)	20.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methylcellulose phthalate is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / Capsule
Soybean oil	280.0
Omeprazole	20.0
Meglumine	20.0
Lecithin	30.0

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule;

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 2

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	30.0
Glycerin	15.0
Water	20.0
Hydroxypropyl methyl cellulose phthalate	10.0
Ammonia solution (25%w/v)	25.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament :

Name of the ingredient	mg / Capsule
Soybean oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Lecithin	30.0mg

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 3

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	40.0
Glycerin	17.5
Water	20.0
Hydroxypropyl methyl cellulose phthalate	5.0
Ammonia solution (25%w/v)	17.5

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / Capsule
Soybean oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Lecithin	30.0mg

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 4

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	17.5
Water	25.0
Hydroxypropyl methyl cellulose phthalate	7.5
Ammonia solution (25%w/v)	15.0

Gelatin mass containing hydroxypropyl methyl cellulose is prepared by dispersing hydroxypropyl methyl cellulose phthalate in the form of a fine powder in a mixture of glycerin and water maintained at 70°C in which gelatin is dispersed to dissolve forming the gelatin mass. After cooling the mass to 45°C, ammonia solution is added slowly along the stirrer rod while stirring into the gelatin preparation tank. Stirring is continued till hydroxypropyl methyl cellulose phthalate is completely dissolved. The mass is made bubble free by applying vacuum while maintaining the mass at 45 - 50°C under continuous mixing.

b) Composition of the medicament:

Name of the ingredient	mg / capsule
Soybean oil	200.0mg
Cremohor RH 40	40.0mg
Lansoprazole	30.0mg
Disodium hydrogen orthophosphate Anhydrous	30.0mg

Cremophor RH 40 is dispersed in soybean oil at 30°C. After cooling to room temperature Lansoprazole and disodium hydrogen orthophosphate are dispersed in to the mixture in the form of fine particles with the help of a mechanical stirrer and / or a homogeniser.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 5

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	15.0
Water	20.0
Hydroxypropyl methyl cellulose phthalate	10.0
Sodium hydroxide solution 1% w/v	20.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved by stirring in to sodium hydroxide solution at room temperature. Hydroxypropyl methyl cellulose phthalate solution in ammonia is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / capsule
Soybean oil	200.0mg
Hydrogenated vegetable oil	85.0mg
Lecithin	20.0mg
Pantoprazole Sodium	45.0mg
Meglumine	20.0mg

Hydrogenated vegetable oil is melted and dispersed into soybean oil at 30 - 40°C followed by lecithin, meglumine and pantoprazole sodium and cooled to room temperature. The mixture is kneaded into a smooth paste using a triple roller mill.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 6

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	30.0
Propylene glycol	15.0
Water	20.0
Hydroxypropyl methyl cellulose phthalate	10.0

Gelatin mass is prepared by dispersing in water at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved in propylene glycol at 60 - 70°C. and mixed with the gelatin mass to obtain uniform mixture.

b) Composition of the medicament:

Name of the ingredient	mg / Capsule
Soybean oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Lecithin	30.0mg

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 7

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	17.5
Water	20.0
Polyvinylacetate phthalate (PVAP)	7.5
Ammonia solution (25%w/v)	20.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Polyvinylacetate phthalate is dissolved by stirring into ammonia solution at room temperature. Polyvinylacetate phthalate solution in ammonia is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / capsule
Sunflower oil	200.0mg
Cremophor RH 40	40.0mg
Lansoprazole	30.0mg
Disodium hydrogen orthophosphate Anhydrous	30.0mg

Cremophor RH 40 is dispersed in sunflower oil at 30°C. After cooling to room temperature Lansoprazole and disodium hydrogen orthophosphate are dispersed into the mixture in the form of fine particles with the help of a mechanical stirrer and / or a homogeniser.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 8

a) **Composition of the Soft gelatin shell:**

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerine	10.0
Triethyl citrate	7.5
Water	20.0
Methacrylic acid co-polymer Type - C	7.5
Ammonia solution (25%w/v)	20.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water triethyl citrate and glycerin maintained at 70°C. Methacrylic acid co-polymer Type - C is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) **Composition of the medicament:**

Name of the ingredient	mg / Capsule
Soybean oil	280.0
Omeprazole	20.0
Meglumine	20.0
Colloidal silicon dioxide	6.0

Colloidal silicon dioxide is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) **Manufacturing of capsule;**

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

EXAMPLE – 9

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	30.0
Glycerin	15.0
Water	20.0
Polyvinyl acetate phthalate	10.0
Ammonia solution (25%w/v)	25.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Polyvinyl acetate phthalate is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament :

Name of the ingredient	mg / Capsule
Sun flower oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Lecithin	30.0mg

Lecithin is dispersed into Sun flower oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

EXAMPLE – 10

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	40.0
Triethyl citrate	7.5
Glycerin	10.0
Water	20.0
Methacrylic acid co-polymer Type - A	7.5
Ammonia solution (25%w/v)	17.5

Gelatin mass is prepared by dispersing gelatin in a mixture of water Triethyl citrate and glycerin maintained at 70°C. Methacrylic acid co-polymer Type - A is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / Capsule
Soybean oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Colloidal silicon dioxide	30.0mg

Colloidal silicon dioxide is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

The advantages of the present invention are:

1) Simple method of manufacturing, when compared to the methods disclosed in the prior art making the process economical.

2) Improved bioavailability when compared to the solid enteric coated pellets and tablets as the medicament is solublised or suspended in the form of very fine particles in the liquid / semisolid pharmaceutical composition filled into the soft gel capsule.

3) The reactive acidic groups of enteric polymers are in minimal contact with the active ingredient as the polymer is mixed into large amount of gelatin mass. Only small amounts of alkaline reactive material is required to neutralize the free fatty acids in the oily substances and free acidic reacting groups of enteric polymer in contact with the active ingredient on inner surface of the shell.

4) The soft gel does not require any protective sub-coating. Consequently the active ingredient quickly dissolves into the intestinal fluid once the gastric resistant but intestinal soluble gelatin composition is dissolved.

5) The soft gel capsules are simple in composition and therefore do not require any sophisticated equipment for manufacturing.

We claim:

1. A pharmaceutical composition in form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments which comprises of a gelatin shell resistant to gastric juice and soluble in intestine having an enteric polymer mixed into gelatin in the form of free acid or its salt and the capsule incorporating a composition comprising of benzimidazole derivative, a hydrophobic oily substance or a mixture of such oily substances, an alkaline inert reacting material, a suspending agent, a surface active agent and / or a solublising agent; wherein the capsules are insoluble in aqueous medium up to a pH of 5.5 but quickly dissolving above pH of 6.0.

2. A pharmaceutical composition as claimed in claim 1 wherein the benzimidazole derivative, is selected from medicaments such as omeprazole, lansoprazole, pantoprazole, timoprazole and the like and the amount present in the formulation is equivalent to one unit dose of selected benzimidazole derivative.

3. A pharmaceutical composition as claimed in claim[s] 1 [& 2] wherein the enteric polymer employed for coating the gelatin shell is selected from polymers such as hydroxypropyl methyl cellulose phthalate, alkyl methacrylate and methacrylic acid copolymers, polyvinyl acetate phthalate and the like in the form of free acid or their ammonia or alkali metal salts and the amount employed ranging from 5.0 to 40.0 percent, preferably 5.0 to 25.0 percent by weight, with reference to the dried shell.

4. A pharmaceutical composition as claimed in claim[s] 1 [to 3] wherein the benzimidazole derivative in the formulation is suspended / solubilised in a hydrophobic oily substance selected from fats and oils of vegetable origin such as sesame oil, corn oil, maize oil, soybean oil, sunflower oil, arachis oil, gingly oil and the like; animal origin such as fish oil, pig oil, beef oil and the like; esters of straight chain aliphatic oils such as Sunsoft 700 P-2 (Taiho chemical company) Panasete 810 (Nippon oils and Fats); hydrogenated vegetable oils or a mixture thereof and the amount of hydrophobic oily substance used ranging from 50.0 to 80.0 percent by weight, with reference to the contents filled in capsules.

5. A pharmaceutical composition as claimed in claim[s] 1 [to 4] wherein substances such ascolloidal silicon dioxide, polyvinylpyrrolidone are used as dispersing agents in an amount ranging from 0.5 to 20.0 percent preferably 1.0 to 10.0 percent by weight and materials such as glyceryl monostearate, lecithin, polyoxyethylene castor oil derivative such as Cremophor RH 40, Cremophor EL (BASF) polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulphate, docusate sodium and the like are used as surface active agent and / or a solublising agent and the amount of surface active agent and/or solublising agent ranging from 2.0 to 20.0 percent, preferably 5.0 to 15.0 percent by weight, with reference to the contents filled in capsule.

6. A pharmaceutical composition as claimed in claim[s] 1 [to 5] wherein materials such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid, other suitable organic or inorganic acids; substances used in antacid preparations; meglumine; triethanolamine and the like are used as alkaline inert reacting materials and the amount ranging from 5.0 to 40.0 percent, preferably 10.0 to 25.0 percent by weight, with reference to the contents filled in capsule.

7. A pharmaceutical composition as claimed in claim[s] 1 [to 6] wherein the soft gel capsules are treated with a gelatin cross linking agent such as formaldehyde, glutaraldehyde, crotonaldehyde, 1,2-phthalic acid aldehyde, 1,3-phthalic acid aldehyde, 1,4-phthalic acid aldehyde; carboimides such as 1-ethyl-3-[2-morpholinyl-(4)-ethyl]-carboimide-metho-P-toluene-sulfonate and the like.

8. A pharmaceutical composition as claimed in claim[s] 1 [to 7] wherein the soft gel capsules are treated with cold dilute solutions of acids selected from hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid, citric acid, propionic acid, benzoic acid, oxalic acid, maleic acid, fumaric acid and the like.

9. A process for the preparation of a pharmaceutical composition in the form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments

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(54) Title: AN IMPROVED PHARMACEUTICAL COMPOSITION AND A PROCESS FOR ITS PREPARATION

(57) Abstract: The present invention relates to an improved pharmaceutical composition, in the form of a soft gel capsule resistant to digestive juice. The composition of the present invention is made up of gelatin and an enteric polymer in the form of free acid or its salts, containing a benzimidazole derivative used in the treatment of duodenal ulcers, solubilised and/or suspended in a liquid or semisolid medium, comprising of a hydrophobic carrier, an alkaline inert reacting material and a surface active agent and/or a solubilising agent. The present invention also relates to a method for preparing the above said pharmaceutical composition.

Attorney Docket No. 13102.6USWO

MERCHANT & GOULD P.C.

United States Patent Application

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that

I verily believe I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: AN IMPROVED PHARMACEUTICAL COMPOSITION AND A PROCESS FOR ITS PREPARATION

The specification of which
a. ☐ is attached hereto
b. ☒ was filed on March 29, 2002 as application serial no. 10/089611 and was amended on (if applicable) (in the case of a PCT-filed application) described and claimed in international no. PCT/IN00/00079 filed August 25, 2002 and as amended on (if any), which I have reviewed and for which I solicit a United States patent.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on the basis of which priority is claimed:

a. ☐ no such applications have been filed.
b. ☒ such applications have been filed as follows:

FOREIGN APPLICATION(S), IF ANY, CLAIMING PRIORITY UNDER 35 USC § 119			
COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)
INDIA	968/MAS/99	1-OCTOBER-1999	
ALL FOREIGN APPLICATION(S), IF ANY, FILED BEFORE THE PRIORITY APPLICATION(S)			
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I hereby claim the benefit under Title 35, United States Code, § 120/365 of any United States and PCT international application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

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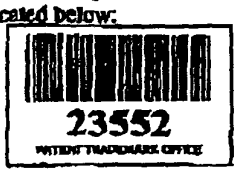

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2-00

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§ 1.56 Duty to disclose information material to patentability.

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

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(2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office, or

(ii) Asserting an argument of patentability.

A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

(c) Individuals associated with the filing or prosecution of a patent application within the meaning of this section are:

(1) Each inventor named in the application:

(2) Each attorney or agent who prepares or prosecutes the application; and

(3) Every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.

(d) Individuals other than the attorney, agent or inventor may comply with this section by disclosing information to the attorney, agent, or inventor.

(e) In any continuation-in-part application, the duty under this section includes the duty to disclose to the Office all information known to the person to be material to patentability, as defined in paragraph (b) of this section, which became available betwee the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

[redacted]